What can evolutionary theory tell us about chronic pain?

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It is 150 years since Darwin published *On the origin of species*, but his insights and others that followed are underused in the study of pain. Understanding of evolutionary processes could help us frame questions and interpret data more coherently, and could provide a translational framework across research endeavours. Common misconceptions about how natural selection operates are widespread; conditions that cause suffering – often painful diseases – are presented as unanswerable challenges to evolutionary theory, but genes spread when they confer a reproductive advantage and/or survival advantage, not because they guarantee health and happiness.[6] Some of those advantages applied in our ancestral environment but not our current environment; some came with disadvantages which did not outweigh the advantages (in the ancestral environment). In the field of pain, an explicitly evolutionary framework is rare in developing models or investigating behavior, with some notable exceptions.[21,31,32] Pain research (and medical research in general[25]) largely targets questions concerning (mechanisms rather than those concerning function, in contrast, for instance, to research on social behaviors such as empathy and altruism[26].

Over evolutionary time, injuries from predatory attacks, intra-species conflict and environmental hazards represent a threat to survival and thus lie at the cutting edge of selection pressures. How can we account for our behavior in relation to injury and pain, and the behavior of animals that we use in pain research? The emotional dimension of pain, established in the IASP definition,[13] and given prominence in some models of pain[5,32] and in some clinical settings, is often neglected in nonhuman animal research, despite striking commonalities of behavior.[4,19,21] Emotions, not least negative ones, can be conceptualized as serving to organize and guide goal-directed action, particularly when goals conflict.[24] The relative neglect of motivation in animals obscures possible continuities in behavior, yet across studies of pain in non-human animals (albeit very unevenly covered) such as cephalopods, crustaceans, fish, and particularly in farmed animals and laboratory rodents among mammals,[1,28,32] shared patterns of behavior are described post-injury: reduced foraging and exploratory activity, sparing or guarding the injured area or limb, and memory for and avoidance of cues associated with the injury.[32] Those working with invertebrate models in particular (such as Aplysia e.g. Walters & Moroz (2009)[33] or crustaceans e.g. Dyuizen et al. (2012)[9]) emphasize evolutionarily conserved mechanisms and genes across phyla.

Behavior is very hard to reconstruct from fossil evidence, yet natural selection often acts directly on behavior, which in turn arises from the physiological, cognitive and emotional phenotype of the animal in question, and ultimately from its genotype. The parsimonious assumption must be that not only anatomy and physiology are the result of natural selection, but behavior also.[29] In an overview of evolutionary theory applied to medicine, Nesse and Stearns[25] propose four explanations of "why natural selection has left the body vulnerable to disease". The four explanations fall into two categories (see p38[25]). *Selection is slow* covers the explanations that (1) our evolution has left us with mismatches with the modern environment; and (2) that pathogens co-evolve with their hosts. *Selection is limited* covers the explanations that (3) there are constraints on what selection can do, or levers for it to act on; and (4) that there are trade-offs between benefits of different characteristics.

They add two further points to correct common misunderstandings: that selection maximizes reproductive success, not overall health; and that the usefulness of defences such as pain and fever outweighs the suffering they cause. The last encapsulates the common belief that acute pain is purposeful whereas chronic pain is

purposeless, an inevitable cost of an almost fail-safe alarm system that has assured our survival. The difficult and shortened lives of people born congenitally insensitive to pain demonstrates that.[23] The clinical implication of the 'inevitable cost' argument is that we are unlikely to find completely effective treatment for chronic pain without undesirable effects on the acute pain system. Is it a sufficient explanation that chronic pain is unavoidable? Or should we consider the other explanations of Nesse and Stearns in relation to pain? I argue that we should, on empirical and theoretical grounds elaborated around two objections.

The first objection is that, if chronic pain is an inevitable result of acute pain, we should expect to see chronic pain in non-human animals, and so we do in some cases. There are accounts of chronic pain (and attempts to prevent or treat it) in companion (pet) and farm animals, but not, apparently, in wild animals[10] (Finlay[10], however, draws the curious conclusion that therefore chronic pain exists to elicit help). It is impossible to tell if this is a gap in the literature or reality in the natural world. Observing wild animals is difficult, as is confidently ascribing their behavior to pain. However, given the excellent observations of some of our nearest relatives, chimpanzees, bonobos, and other primates, in the wild and in semi-wild reservations, with descriptions of healed injuries[11,14,15] and of adjustment to disabilities,[3] there seems to be little interest in the possibility of chronic pain among animals that survive injury.

Wall[31] is one of the few people to describe wild animals after injury, observing in the recovering wounded deer "a solitary inert animal with marked changes of its eating, escape and social behaviour" ([31] p257). In his characterisation of pain as "awareness of a need-state", he describes chronic pain as a phase of resource conservation to maximize healing. Mounting an inflammatory and immune response is very energy-demanding, so reducing other activity, particularly play, exploration, courtship, and mating, not only avoids accidental re-injury but ensures that resources are reserved first for defense. However, the animal must still eat and drink, avoid predators, and stay connected to its family group, troop, or herd. This requires a dynamic balance between resource conservation for healing and resource expenditure for essential survival activities, changing towards the latter as healing progresses and eventually returning to normal.

The only animals that are not compelled by such fundamental needs to regain normal activity, however gradually, are those whose needs are met by others,[10] unlike the wounded deer. Companion and domesticated animals, and humans themselves, have their needs met by humans. This is not a modern phenomenon; fossil remains of early hominids show many to have survived into adulthood despite major injuries.[8,20] Might providing help to those unable to survive unaided, temporarily or permanently, actually prolong the recovery phase? If post-injury sensitization flourishes in the absence of normal sensory experience,s (including proprioception), then it is possible to hypothesize that chronic pain, that is, pain that outlasts healing, may be less likely to develop in the presence of increasing activity. This is consistent with findings on exercise reversing early development of hypersensitivity after nerve injury, a process implicated in chronic neuropathic pain.[2] By contrast, an injured limb or area that is immobilized or isolated, and protected indefinitely from normal sensation and movement, might invite amplification and/or reduced descending inhibition, in turn contributing to the spread of pain? Such a pattern is normally formulated with fear of pain as the fundamental motivation[30] but since pain is inherently threatening this does not advance the explanation. This fits the first of Nesse and Stearns' explanations:[25] a mismatch of evolved adaptations with the modern environment. (The mostly widely cited example of this is obesity: we evolved to seek calorific food and to store fat, but only recently in some societies has the energy cost of seeking and consuming easily available food fallen far short of the energy consumed.)

The second objection is that recent evidence shows that sensitization after injury can be protective and enhance survival. In 2014, Walters and colleagues showed that sensitization following injury in squid changed their behavior such that they were less predated.[7] This finding was so striking that an accompanying editorial by Price and Dussor[27] commented that "These findings have profound implications for pain neuroscientists and clinicians and, we will argue, for neurobiology in general."([27] R384).

Half the squid in the Crook et al. study[7] were injured by removal of the end of one arm, but some of those received local anesthesia that prevents the development of sensitization. Controls, injected with local anesthetic or merely handled, were not injured. Six hours later, recovered and swimming apparently normally, they were put in a tank with black bass, a predator. Bass selectively pursued the injured squid (predators commonly target animals moving abnormally[32]): those that had received local anesthetic and had no sensitization were more effectively predated; those with sensitization were more alert to the threat of predation and initiated escape behaviors earlier. Significantly more of the sensitized squid survived the half hour exposure to predation, and the authors comment that their findings strongly support the hypothesis of "persistent hyperexcitability mechanisms" as evolved adaptations following injury. Perhaps we should reformulate "fearavoidance" [30] in humans with pain as similar risk-aversion.

This study begins to address the question of what were the challenges that our neural mechanisms of pain evolved to tackle. It needs replicating in other species, and raises many further questions: about possible different functions of sensitization early and late after injury,[32] and about the relationship with memory for cues associated with the injury, an important issue not addressed here. We might ask: how much pain is optimal; what is its function, at any point in the range of experience from a repeated non-noxious stimulus applied to undamaged tissue to soreness and reflex protection of a healing wound as use is regained. And we might ask why, in chronic pain, this mechanism does not subside once healing is complete, for which a possible explanation is discussed above. Walters' extensive studies of sensitization in vertebrates and invertebrates, using evolutionary principles to interpret findings,[32] have produced a classification of adaptive behaviors as immediate, rapid, and delayed (recovery and wound care), similar to the function of pain proposed by Wall.[31] This is not to neglect hypoalgesia in the attack phase[31,32] when resources must be committed to survival so the optimal pain level is zero.

Taking an evolutionary perspective on pain and behavior, not only across species but families and even phyla, requires re-examining the questions we ask and the paradigms we use to answer hem. There is room only for a few diverse examples. The first concerns the low ecological validity of some pain stimuli in research, electric shock and thermal extremes in particular. (The case for ecologically valid responses has been well made[22]). The second asks: in human studies, can healthy (and even rewarded) volunteers experiencing expected and escapable low levels of pain tell us much about emotional processing of pain? It is rare for studies to demonstrate that they create threat (though see Wiech et al. (2010)[34]). Third, are the vigilance, inactivity, and withdrawal from social interactions (as observed in wounded animals[31]) of people with persistent pain better understood as over- applied adaptations than as maladaptation or pathology? Fourth, in observational assessment of pain (such as by clinicians), why is matching the self-rating of the person in pain used as the criterion, when there could be no selective pressures for this degree of accuracy, only for some discrimination between more or less severe pain?[35] Fifth, we should be alert to the effects of social context, including possible sex differences, on threat experiences in humans or non-human animals, and consider including them in pain studies.[16,17] Even these by no means exhaustive examples are relevant to much pain research.

If we conceptualize pain mechanisms in relation to the challenges that they evolved to tackle, such as that sensitization functions to promote healing by making it aversive to use an injured body part, then we should address cognitive and emotional processing in the same context. Unifying models of processing incoming signals (e.g. Friston (2010)[12] and Legrain et al. (2011)[18]), not limited to human psychology, are more promising for understanding pain in the wider field of neurobiology than are many current abstract concepts in pain psychology.

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